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09/601,168	07/28/2000	RICHARD BENAROUS	935.38812X00	8585

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SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	FILED 09/01/01	Application No. 09/601,168	Applicant(s) BENAROUS ET AL.
		Examiner Holly Schnizer	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 25 April 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-7 and 22-50 is/are pending in the application.

4a) Of the above claim(s) 6,22-26,28-30,33-36 and 38-50 is/are withdrawn from consideration.

5) Claim(s) 3-5 is/are allowed.

6) Claim(s) 2,7,27,31,32 and 37 is/are rejected.

7) Claim(s) 1 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 29 January 1999 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 4) Interview Summary (PTO-413) Paper No(s). _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-5, 7, 27, 31, 32, and 37 in Paper No. 8, filed April 25, 2002 is acknowledged. The traversal is on the ground(s) that all of the inventions of Groups 1-27 are linked and relate to a single inventive concept, the human β -TrCP. This is not found persuasive because as stated in the Restriction mailed March 25, 2002 (Paper No. 7), pursuant to 37 C.F.R. 1.475(d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto.

Accordingly, the main invention (Group 1) comprises the first-recited product, a human β TrCP protein of SEQ ID NO:2, the nucleic acid encoding it, a vector comprising said nucleic acid molecule, a host cell comprising said vector, and a method of using the protein to identify anti-HIV-1 agents. Further, pursuant to 37 C.F.R. 1.475(d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention. Thus, the separate products and methods of Groups 2-27 define separate inventions.

The requirement is still deemed proper and is therefore made FINAL.

Status of the Claims

Claims 1-7 and 22-50 are pending. Claims 6, 22-26, 28-30, 33-36, and 38-50 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-5, 7, 27, 31, 32, and 37 will be considered in this Office Action.

Specification

The Specification is objected to for the recitation of amino acid sequences without reference to a sequence identifier (see page 5, line 16 and 18; see also claim 2). Sequences of greater than 4 amino acids in length must be identified by a sequence identifier (SEQ ID NO:) (see MPEP 2422 and 37 C.F.R. 1.821).

Claim Objections

Claim 1 should refer to the sequence identifier as "SEQ ID NO:2" as indicated in 37 C.F.R. 1.821(d) rather than as "SEQ ID No. 2" as is presently claimed. Correction is required.

Claims 7, 31, and 32 are objected to because they encompass polynucleotides encoding peptides devoid of the F box and peptides devoid of WD units and therefore encompass non-elected subject matter. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 2, the phrase "especially" renders the claim indefinite because it

✓ is unclear whether the limitations following the phrase are part of the claimed invention.

See MPEP § 2173.05(d).

✓ Claim 5 is unclear as to what sequence the amino acid positions listed in the claim refer. Do the amino acid positions correspond to SEQ ID NO:2?

✓ Claim 27 is indefinite because it is drawn to the peptide fragments of Claim 7 whereas Claim 7 is drawn to nucleic acid sequences. Correction is required.

Claim 27 is also indefinite as to what is meant by "which have conserved both the WD units and the F-box". Many proteins have WD units and F-boxes with varying sequences. Therefore, the claim is unclear as to whether the peptide fragments claimed have the WD units and F-boxes with sequences of SEQ ID NO:2 or if they are only limited to any F-box or WD unit sequence. Clarification is required.

Claim 37 is unclear as to the nexus between the capability of the anti-HIV antiviral agent candidates to inhibit the interaction between human β-TrCP protein and Vpu protein and identifying the candidate as an anti-HIV-1 antiviral agent. The goal of the method ("identifying anti-HIV-1 antiviral agents") appears to be different from that of the endpoint (determining "the capability of the anti-HIV antiviral agent candidates to inhibit the interaction between h-βTrCP protein and Vpu protein"). Thus, the claim is

unclear as to which of the candidates that inhibit the interaction between h- β TrCP protein and Vpu protein is considered an anti-HIV-1 antiviral agent. Furthermore, the claim is unclear as to how the h- β TrCP protein is used in screening. What is the screening step; screening for activity, for binding, for inhibition of h- β TrCP binding to Vpu? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 27, 31, 32, and 37 are rejected under 35 U.S.C. 112, first paragraph because while being enabling for the human β -TrCP protein having the sequence of SEQ ID NO:2, the polynucleotide encoding the human β -TrCP protein having the sequence of SEQ ID NO:2 (including the polynucleotide of SEQ ID NO: 1), the polynucleotide encoding a β -TrCP protein containing the deletions disclosed in the specification (deletion of the F-box or deletion of the first WD domain, for example), and a method of identifying anti-HIV-1 antiviral agents comprising the step of determining whether an anti-HIV antiviral agent candidate can inhibit the interaction between h- β TrCP and Vpu wherein the candidates that inhibit the interaction are identified as anti-HIV-1 antiviral agents, the specification does not reasonably provide enablement for 1) a nucleic acid sequence coding for a peptide fragment that results from addition, deletion and/or replacement of one or more amino acids of a β -TrCP protein characterized in that it consists of (a) a DNA sequence of the nucleic acid fragment

coding for said peptide fragment (clm 7a), or (b) a DNA sequence that hybridizes with the above sequence or one of its fragments (clm. 7b), or (c) a DNA sequence which results from the sequences (a) and (b) and codes for the human β -TrCP fragments (clm. 7c), **2)** expression vectors (clm 31) or host cells (clm 32) containing the nucleic acid sequences, or **3)** antitumoral agents which consist of the peptide fragments of the human β -TrCP protein (clm 27).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims, as indicated in the previous Office action.

The state of the art is such that it is acknowledged that amino acid modifications of proteins is unpredictable. One cannot merely predict protein function from amino acid sequence information or from amino acid sequence similarity to other related proteins. While it is known that many amino acid substitutions are generally possible in

any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16). The instant claims encompass nucleic acid sequences encoding proteins which have any number of amino acid substitutions, deletions, or alterations (as implied by the phrase "or a peptide fragment that results from the addition, deletion and/or replacement of one or more amino acids"). However, Applicant has only provided guidance as to a single sequence of a β -TrCP protein (SEQ ID NO:2) and a few deletion mutants wherein the entire F-box or individual WD domains have been deleted and has not provided any guidance as to what amino acids within the protein sequence may be replaced or added. Thus, the present specification does not enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification provides a assays for screening for determining what effect a modification has on protein binding, this is not adequate guidance as to the nature of the β -TrCP molecules that may be

constructed, but is merely an invitation to the artisan to use the disclosed protein as a starting point for further experimentation.

In addition, the specification does not enable one of skill in the art to use the β -TrCP proteins, especially the innumerable fragments with any number of amino acid modifications, as an antitumoral agent as claimed in Claim 27. The specification has only shown that the protein of the invention (SEQ ID NO:2) can bind other proteins involved in the cell cycle but has not shown how the protein of the invention is related to any disease state. There are many proteins like β -TrCP that have F-boxes and WD domains and that appear to be involved in the ubiquitin pathway by binding the same proteins as β -TrCP (see Skowyra et al. Cell (1997) 91: 209-219 at page 217, Fig. 6 and p. 217, Col. 2, paragraph 2). However, while those of skill in the art appear to acknowledge the potential of these F-box proteins in the development of drugs, (see Hatakeyama et al. Proc. Natl. Acad. Sci (1999) 96: 3859-3863 at p. 3862, Col. 2, last paragraph through p. 3863, Col. 1, first paragraph) it is understood in the art that elucidation of the biochemistry of the ubiquitin pathway is necessary in order to use these proteins in any therapeutic application (see Skowyra et al. p. 217, Col. 2, lines 30-37 and Hatakeyama et al. p. 3863, Col. 1, first paragraph). In the present case, the specification only shows how the protein of the invention interacts with individual proteins and does not show how this interaction affects the entire cascade of proteins involved in ubiquitination or the cell cycle. Moreover, the specification does not show what effect the protein of the invention has on the cell cycle or on tumors. Thus, in order to practice the claimed invention, one of skill in the art would be required to

characterize the effect of the β -TrCP protein of the invention on tumor growth. Such experimentation is considered undue since it would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner.

Due to the large quantity of experimentation necessary to generate the infinite number of β -TrCP molecules recited in the claims and possibly screen same for activity and determine their potential as antitumoral agents, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed β -TrCP protein are required for the functional and structural integrity of the protein and the characterization of their effect on tumor growth. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 27, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written Guidelines published January 5, 2001 in the Federal Register, Vol. 66, No. 4, p. 1099-1111 (available at www.uspto.gov) and the Examiner training Materials on Written Description also available at www.uspto.gov.

The claims are drawn to a genus of nucleic acid sequences coding for a peptide fragment of human-bTrcp having any number of amino acid additions, deletions, and/or replacements. Claims 27, 31, and 32 are dependent on Claim 7 and have any of the nucleic acid sequences disclosed therein. The only limits on the number of amino acid modifications that may be made are that the resulting fragment maintains the activity of interacting with the Vpu protein of HIV-1, the cell protein I kB, or the cell protein β-catenin and /or with the skp1p protein. Parts a, b, and c, are not considered to further limit the claim since they only recite DNA sequences already mentioned in the main part of the claim . Thus, the claim is considered to be drawn to any nucleic acid sequence that codes for a protein having the activity of interacting with the Vpu protein of HIV-1, the cell protein I kB, the cell protein β-catenin, or the skp1p protein. The specification discloses a single β-TrCP protein of SEQ ID NO:2 and various modifications of SEQ ID

NO:2 wherein a single domain is removed (i.e. SEQ ID NO:2 without an F-box or SEQ ID NO:2 without the first WD domain). The specification and claims do not provide any guidance with respect to the relationship between specific amino acids within the sequence and function. For example, there is no guidance as to what effect changing amino acids within the F-box would have on skp1p binding. The Specification indicates that such changes could affect the binding. For example, page 2 of the Specification states "it is not certain that the function of the homologous proteins will be totally conserved. Moreover, there are numerous examples which show that there are always significant differences between species" (p. 2, lines 4-6). Thus, the Specification acknowledges that even two highly homologous proteins may not have identical function. However, the Specification does not teach what identifying characteristics of the sequence of the protein of the present invention give it its identifying function. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely and is little more than a wish for possession (see Fed. Reg. (2001) Vol. 66(4) p. 1110, Col. 2, citation 49 citing Eli Lilly, 43 USPQ2d at 1406)).

In addition, the specification and claims do not provide any structural or functional characteristics to distinguish a human β-TrCP from that of other species or proteins that have different functions. For example, Hatakeyama et al. (Proc. Natl. Acad. Sci. (1999) 96: 3859-3863), Skowyra et al. (Cell (1997) 91: 209-219) disclose

proteins that appear to have the function of the protein of the claimed invention (clm7), that of binding skp1p. The specification does not provide guidance as to whether these proteins of similar function and structure to that of the protein of the present invention are considered modified β-TrCP proteins. Similarly, the specification acknowledges that the previously identified slimb protein and β-TrCP of Xenope are homologs of the protein of the present invention (p.1 lines 19-35). However, the specification does not provide any structural or functional characteristics of a "human" β-TrCP protein so as to distinguish it from homologs from other species.

Therefore, the scope of the claims include innumerable structural variants (nucleic acid sequences and antiviral agents) and the genus is highly variant because a significant number of structural differences between genus members is permitted. There is no description of mutational sites that exist in nature, and there is no description of how the structure of the specific SEQ ID NO: relates to the function of the protein or disease. Thus, the common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of such a large genus is not representative of the variants of the genus and is insufficient to support the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 7, 31, and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Skowyra et al. (Cell (1997) 91: 209-219).

Skowyra et al. disclose nucleic acid molecules coding for peptide fragments resulting from the addition, deletion, and replacement of one or more amino acids of the human protein h-bTrcp. Both Grr1 (see abstract) and cdc53 (see Fig. 6) bind Skp1 protein and both of the nucleic acid molecules encoding both of these proteins was used in expression assays (see Table 1). The disclosed nucleic acid sequences encoding the peptide fragments were contained in viral expression vectors (clm 31) and expressed in insect host cells (clm 32) (see p. 217, Col. 2 through p. 218, "Purification and Phosphorylation of Recombinant Proteins"). Thus, the Skowra et al. reference is considered to meet the limitations of Claims 7, 31, and 32.

Claims 7, 31, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bour et al. (J. Virol. (1995) 69(3): 1510-1520).

Bour et al. disclose nucleic acid molecules coding for peptide fragments resulting from the addition, deletion, and replacement of one or more amino acids of the human protein h-bTrcp. Bour et al. show that the encoded protein, CD4 binds Vpu (see abstract). Bour et al. describe an expression vector that expresses CD4 and HeLa cells (host cells) containing the expression vector (see Materials and Methods, "Recombinant DNA Constructs", p. 1511). Thus, it appears that the Bour et al. reference meets the limitations of claims 7, 31, and 32.

Claims 7, 31, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Rubinfeld et al. (J. Biol. Chem. (1995) 270(10): 5549-5555).

Rubinfeld et al. disclose a nucleic acid sequence coding for a peptide fragment considered to be resulting from the addition, deletion, and replacement of amino acids of the human protein h-b-TrCP. The nucleic acid sequence encoding the APC protein disclosed in Rubinfeld et al. is considered patentably indistinguishable from that of Claim 7a, c, and d since the resulting protein, APC, binds β -catenin, since it has a sequence that could result from the addition, deletion, and replacement of amino acids in the human h-b-TrCP. Rubinfeld describe an expression vector that expresses the APC protein in yeast and in insects (see Materials and Methods). Thus, it appears that the Rubinfeld et al. reference meets the limitations of Claim 7, 31, and 32.

Claims 7 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Inoue et al. (Proc. Natl. Acad. Sci. (1992) 89: 4333-4337).

Inoue et al. disclose a nucleic acid sequence coding for a peptide fragment considered to be resulting from the addition, deletion, and replacement of amino acids of the human protein h-b-TrCP. The nucleic acid sequence encoding the Rel protein disclosed in Inoue et al is considered patentably indistinguishable from that of Claim 7a, c, and d since the resulting protein, Rel, binds I κ B (see Fig. 5a, lanes 1 and 3) and since it has a sequence that could result from the addition, deletion, and replacement of amino acids in the human h-b-TrCP. Inoue et al describe an expression vector that expresses the Rel protein (see Materials and Methods, "Protein-Protein Association

Assay). Thus, it appears that the Rubinfeld et al. reference meets the limitations of Claim 7, 31, and 32.

Conclusions

Claim 1 would be allowable if amended to overcome the objection given above. Claims 3-5 appear to be in condition for allowance. A thorough search of the prior art did not reveal any teaching or suggestions of a protein having the sequence of SEQ ID NO:2.

Claims 2, 7, 27, 31, 32, and 37 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Holly Schnizer
July 10, 2002

Christopher S. F. Low
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